Comments on

CHMP Guideline on Clinical Investigation of Medicinal Products for the Treatment of Social Anxiety Disorder (SAD)
(CHMP/EWP/3635/03, Draft, 18 November 2004)

German Region of the International Biometric Society

Comments:

1. page 5-6, 2.3. Methods to assess efficacy

This chapter states that '… effect should be addressed in terms of clinical relevance (responders, remitters) …..'. The section might be misleading and could be interpreted that a responder criterion is requested for primary analysis and that the difference between the responders should be clinically relevant. The section should be clarified. See also our comments 2., 4., and 5. on related issues.

2. page 6, 2.4. Primary efficacy endpoints, 3rd paragraph, 1st sentence

'Improvement of symptomatology should be documented as a difference between baseline and post-treatment score, however, in order to allow an estimate of clinical relevance the proportion of responders or remitters should be presented.'

The term 'clinical relevance' could be interpreted in two ways - clinically relevant difference between groups or clinical relevant improvement from baseline. The wording suggests the first interpretation, although the latter seems to be reasonable. It should be made clear what is meant.

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3. page 7, 4.2.1.1 Choice of control group, 1st paragraph

This chapter states that 'the test product should be compared with both placebo and an active comparator, using a three- or multi-arm design. …The aim of the study may be superiority over placebo or active comparator, non-inferiority against active comparator, or at least demonstration of a similar balance between benefit and risk of the test product in comparison to an acknowledged standard agent.'

If the aim of the study is to show superiority over an active comparator, we do not see the necessity to include a placebo arm.

4. page 8, 4.2.1.3 Methodological considerations, 2nd sentence

‚Sample size should be calculated based on an effect size that is clinically relevant. It may be useful to take the clinical relevance (responders/remitters) into consideration.'

It is not clear what this means exactly. There are several alternatives:

(A) Is it recommended to choose the effect size used for sample size calculation not too small for testing against the null hypothesis that the effect is equal to zero?

(B) Is it required to perform a so-called responder analysis, e.g. to show that the rate of patients achieving a pre-defined clinically relevant improvement is significantly larger in the test drug group as compared to control? This approach is often regarded as problematic because of the somewhat arbitrary definition of the cutpoint and the loss of information resulting from dichotomization.

(C) Is it required to show that the effect is significantly greater than a clinically relevant difference greater than zero (test of a shifted null hypothesis)? This approach often results in an enormous increase in sample size.

(D) Is it required to show that the effect is significantly greater than zero and that the observed effect is greater than a clinically relevant difference? This approach was recently recommended by Kieser and Hauschke (to appear in Pharmaceutical Statistics, 2005).

The requirements should be specified more precisely.

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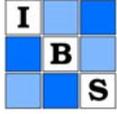
5. page 8, 4.2.1.3 Methodological considerations, Last sentence

'However, it may be considered that clinical assessment of significant effects is done by inspection of the clinical relevant improvement from baseline on the primary outcome measure defined by remitters/responders.'

It is not clear what is meant by this sentence.